

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Multiple Sclerosis: Differential Diagnosis

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For attachment 1

INTRODUCTION

Practically every one of my patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) was referred to me with the diagnosis of multiple sclerosis (MS). Most often this diagnosis had been based exclusively on the presence of some areas of increased signal intensity on T2-weighted MRIs. At times, it was the presence of paresthesiae, and in a few cases it had been made because of abnormal neurologic signs in combination with MRI findings. Both ME/CFS and MS are much more common in young women than in men, and the age of onset in both diseases usually occurs in the third and fourth decades. There are fluctuations in the severity of the symptoms of ME/CFS which may mimic the relapses and remissions of MS, and, unfortunately, both diseases still retain an aura of mystery which more often than not leads to extensive, expensive and fruitless laboratory investigation. Both conditions seem to be triggered by nonspecific mild, presumably viral infections. Behan (1) has provided an excellent description of ME that is most helpful in the differential diagnosis of MS: "The afflicted patients, normally young women, have a wide variety of complaints but these always include muscle pain, generalized weakness and exhaustion. The illness starts acutely with headache and deep muscular pains and patients often feel lightheaded and complain of generalized lassitude and exhaustion and also of subjective sensory phenomena. Once the illness is established, neurological examination may reveal muscle twitching and localized muscle weakness. The muscle weakness may vary in intensity and change from muscle to muscle. These neurological signs are most often of a fleeting nature".

SIGNS AND SYMPTOMS OF INVOLVEMENT OF THE NERVOUS SYSTEM IN ME/CFS

The specific symptoms of involvement of the nervous system in ME/CFS are amazingly varied. With the exception of headaches, no neurologic sign or symptom is included in any of the several published diagnostic criteria (2-7). Indeed, some of the more serious neurologic symptoms that have been reported remain controversial. This is particularly true regarding seizures. Komaroff (8) and Buchwald et al. (6) mentioned them in a very few patients, but Behan (9) stated that seizures do not occur in the disease. Neurologic signs and symptoms in ME/CFS are mentioned by several authors, but most often without enough descriptive data to allow for critical evaluation.

Paresis, diplopia, urinary retention, facial paresis and the Babinski sign are mentioned by Henderson and Shelokov (10) in their review of the signs and symptoms present in patients in 23 epidemics. Acheson (11) also cited similar findings in his literature review. Komaroff (8) and Buchwald et al. (6) listed ataxia, focal weakness and transient blindness. Pelfew (12) underlined the importance of using caution in interpreting neurologic symptoms when he said, "A patient examined in the morning might have nystagmus which would disappear at mid-day, recur later, disappear later, and recur next day. This on again-off again pattern is typical of ME/CFS. Perhaps more relevant is the fact that Lane (13) and Behan et al. (14) both neurologists, found no neurologic abnormalities in their ME/CFS patients; neither did Buchwald et al. (15) in their analysis of 103 ME/CFS patients.

Magnetic resonance imaging studies (MRI) revealed areas of increased signal intensity in the white matter of the CNS in ME/CFS patients. In general these are punctate in size, scattered throughout the white matter but more commonly located at the periphery, near the white-gray junction rather than in the periventricular areas. Changes in cerebrospinal fluid (CSF) have also been reported. Warner et al. (16) found leukocytosis, elevated IgG synthesis and CSF oligoclonal bands in a very few patients. Abnormal visual evoked potential studies have also been reported.

In summary, it is clear that the neurologic signs and symptoms that can be noted in MS also occur in ME/CFS. Similarly, mild abnormalities of laboratory procedures, in particular MRI, also are found. Many of the reports mentioning these abnormal neurologic signs and symptoms describe them only vaguely, making it extremely difficult to determine the exact frequency with which they occur in ME/CFS.

THE DIFFERENTIAL DIAGNOSIS BETWEEN ME/CFS AND MS

MS is distinguished by many neurologic symptoms, and the diagnosis is based on the occurrence of these symptoms in characteristic constellations. One essential criterion is dissemination in space, i.e., evidence of the presence of multiple lesions, but a diagnosis cannot be made until additional symptoms appear in order to fulfill the criterion of dissemination in time. Not only are the characteristic initial symptoms of MS extremely unusual in ME/CFS, but a clear-cut history of real exacerbations and remission is also uncommon. It is rare for ME/CFS patients to have abnormal neurologic

signs. These, on the other hand, are quite common in MS patients. These signs include unilateral loss of vision with a central scotoma; unilateral, acquired red-green color blindness; Marcus Gunn phenomenon; documented internuclear ophthalmoplegia; Uthoff's phenomenon; acute transverse myelitis; urinary and/or bowel incontinence; mono- or hemiparesis and paresthesia or paralysis; Babinski signs; hand incoordination; true gait and/or truncal ataxia; foot drop, asymmetrical anatomically correct sensory changes; Lhermitte symptom; the sensory useless hand; anatomically correct radicular pains; hemifacial spasms and trigeminal neuralgia. The onset of MS is never associated with fever, headaches, chills, malaise, sore throat, backache, vomiting, nausea, diarrhea or lymphadenopathy, all of which are typical initial symptoms of ME/CFS. Generalized weakness is not a complaint of MS patients, nor is transient weakness of single muscle groups, both of which are characteristics of ME/CFS. Tinnitus, also a common observation in ME/CFS, is not encountered in MS, and headaches are not a constant complaint of MS patients, although they do occur in them. Fatigue is only exceptionally a presenting symptom of MS.

Many systemic conditions, including cardiovascular, gastrointestinal, autonomic, and muscular problems, are of great help in differentiating ME/CFS from MS. The fact that the peripheral nervous system and muscle are involved in ME/CFS and not in MS is an important differential point. Acheson (11) has emphasized the fact that "pain, invariably present, may be devastating and is perhaps the feature which impresses itself most forcibly on the observer".

One of the characteristics of ME/CFS is its tendency to occur in epidemics, this is not true of MS. A careful study of some of these reports implied that there was a major element of group susceptibility (17) reminiscent of the Aldous Huxley book *The Devils of Loudun*, a classic commentary on an historical epidemic of St. Vitus dance.

Certain attributes of ME/CFS are very useful in establishing the diagnosis. These have been listed in Table 1, and constitute my own diagnostic criteria for ME/CFS. Migratory myalgias are not seen in MS. With the exception of the common low back pain that is usually secondary to gait disturbances and unequal leg weakness, muscle pains are never seen in MS. Neither are migratory arthralgias or joint pains without any evidence of swelling or inflammation. Migratory paresthesiae, often with a burning, painful sensation, moving from one part of the body to another within a matter of hours or days, are quite different from the pins-and-needles/numbness paresthesiae of MS. The dizziness of ME/CFS is not true vertigo, but is rather lightheadedness. It is often associated with the sensation of disequilibrium, which is quite different from ataxia and is characterized by a concern, even a fear, of a gait disturbance and a possible fall.

The last feature, which consists of unusual reactions to medications, is common but puzzling. Many of the symptoms of ME/CFS do not respond to the use of corticotropin or corticosteroids (a useful differential point from MS), but ME/CFS patients receiving steroids may complain of severe lethargy, itching, even increasing symptoms, in particular pain. Some patients suffer from depression and lethargy with fluoxetine (Prozac) and complain of sleepiness when taking amantadine.

Table 1

Clinical Characteristics of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome

Major Symptoms

- Fatigue
- Migratory myalgias
- Migratory arthralgias
- Migratory painful paresthesiae
- Memory and cognitive disturbances

Minor Symptoms

- Dizziness
- Sensation of dysequilibrium
- Sleep disturbance
- Anhedonia
- Unusual reactions to medications

The combination of fatigue, two of the major and two of the minor symptoms is strongly suggestive of the diagnosis.

dine. Patients also seem to be extremely sensitive to some medications, and have toxic reactions to very small doses of carbamazepine (Tegretol) or phenytoin (Dilantin).

Although in my experience, ME/CFS patients have often been diagnosed as having MS, it is quite likely that some individuals who carry the former diagnosis do suffer from MS or from chronic disseminated encephalomyelitis. The increasing reliance upon laboratory procedures, in particular MRI is responsible for the misdiagnosis of a number of ME/CFS patients as having MS. This indicates that there is no substitute for a careful review of the patient's medical history to correctly differentiate between these two conditions, rather than relying upon laboratory procedures.

SUMMARY

Chronic fatigue syndrome and multiple sclerosis may at times be difficult to differentiate from each other. There are, however, distinct differences and the findings of fever, headaches, chills, diarrhoea and lymphadenopathy, transient weakness of a single muscle, tinnitus, no neurological signs, all strongly suggest chronic fatigue syndrome. Fatigue itself, whilst it occurs in both conditions, is an unusual (but rare) presenting symptom of multiple sclerosis. Systemic involvement including cardiovascular, gastrointestinal, autonomic and muscular problems are perhaps of the greatest help in differentiating ME/CFS from MS.

RIASSUNTO

La sindrome della fatica cronica e la sclerosi multipla sono talvolta difficili da differenziare. Ci sono comunque delle diversità ed il riscontro di febbre, cefalea, brividi, diarrea, linfadenopatia, debolezza transitoria di un singolo muscolo, titinnitus in assenza di segni neurologici, depongono in favore della sindrome della fatica cronica. Il sintomo fatica,

andiose è presente in entrambe le condizioni cliniche, è un insolito (ma raro) segno di presentazione della sclerosi multipla. Il coinvolgimento sistemico, soprattutto a livello cardiovascolare, gastrointestinale, del sistema nervoso autonomo e dell'apparato muscolare, è di grande aiuto per la diagnosi differenziale tra le due malattie.

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